PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/59, 31/56, 31/593, 31/573, A61P 17/06

A1

(11) International Publication Number: WO 00/64450

(43) International Publication Date: 2 November 2000 (02.11.00)

(21) International Application Number: PCT/DK00/00033

(22) International Filing Date: 27 January 2000 (27.01.00)

(30) Priority Data:
PA 1999 00561 23 April 1999 (23.04.99) DK

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract

The present invention relates to a pharmaceutical composition for dermal use, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid.

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PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

The present invention concerns pharmaceutical compositions for dermal use which contain at least one vitamin D or vitamin D analogue and at least one corticosteroid. More specifically, the invention relates to pharmaceutical compositions containing two or more pharmacologically active compounds which have low compatibility with respect to the pH value of optimum stability, preferably, said pharmacologically active compounds are at least one vitamin D analogue and at least one corticosteroid.

BACKGROUND OF THE INVENTION

In the treatment of a number of conditions using dermal application, e.g. in the treatment of psoriasis, it is often indicated to employ a combination treatment incorporating two or even more different pharmacologically active compounds. Thus, in the treatment of e.g. psoriasis, it is common to use a combination treatment involving a steroid compound, such as a corticosteroid compound, and a vitamin D analogue such as calcipotriol, and where each of the active compounds are formulated in separate preparations.

Until now a topical pharmaceutical composition comprising a combination of a vitamin D analogue and a topical steroid has not been described. Moreover, these two types of compounds often have optimum stability values of pH that differ significantly from one another making it non-obvious to attempt to prepare a topical pharmaceutical preparation containing a steroid compound together with a vitamin D analogue. US patent No. 5,565,462 relates to topical pharmaceutical compositions containing certain xanthine compounds, and where said compositions may additionally contain active compounds, such as steroids and vitamin D and its derivatives. However, there is no disclosure of a topical composition containing both a steroid and a vitamin D or vitamin D analogue or derivative, nor is there any description of a method of preparing such a composition.

The following example describes the difficulties encountered when the skilled person wishes to prepare a combination composition for topical use comprising both a

vitamin D or a vitamin D analogue or derivative and a topical steroid: The vitamin D analogue calcipotriol, as well as other examples of vitamin D analogues, requires a pH value above 8 for maximum stability, whereas corticosteroids such as Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) require pH values in the range of 4-6 for maximum stability. Since the base auxiliary materials and additives traditionally used in preparing topical formulations, such as creams and/or ointments, involve having some kind of acid or alkaline nature or reaction ability, it has therefore hitherto not been possible to combine the two active compounds in one single formulation while maintaining good stability of the active compounds.

Consequently, physicians have had to resort to letting patients under this type of two-component regimen perform sequential application of two creams/ointments, each containing one of the compounds formulated at its maximum stability pH. This may lead to incompatibility of the preparations so that patients must, e.g., apply one cream/ointment in the morning and the other in the evening. Needless to say, patient compliance as well as correct administration dosage is a problem under such circumstances. Richards, H.L. et al. report in *J Am Acad Dermatol* 1999 Oct; 41(4):581-3 on a study of patients with psoriasis and their compliance with medication. They report that poor compliance with treatment advice in chronic conditions, such as psoriasis, represents a major challenge to health care professionals: Thirty-nine percent of participants reported that they did not comply with the treatment regimen recommended. The noncompliant group had a higher self-rated severity of psoriasis, were younger, and had a younger age at onset than those who were compliant. The noncompliant group reported that psoriasis had a greater impact on daily life.

It is therefore an object of the present invention to provide a pharmaceutical composition for dermal use where said composition alleviates the inconveniences of a two-component or multi-component regimen for the treatment of psoriasis and other inflammatory skin diseases including nail diseases. The provision of said composition will result in a substantial improvement in quality of life for a large population of psoriasis patients, especially the noncompliant group having a higher self-rated

severity of psoriasis, being younger, and having a younger age at onset than those who are compliant.

SUMMARY OF THE INVENTION

In order to solve the above mentioned problems, the invention provides a pharmaceutical composition for dermal use, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid.

DETAILED DESCRIPTION OF THE INVENTION

As a first pharmacologically active component A it is preferred to use a compound selected from the group consisting of seocalcitol; calcipotriol; calcitriol; tacalcitol, maxacalcitol; paricalcitol; falecalcitriol; 1α,24S-dihydroxy-vitamin D2; and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.

More preferred are vitamin D analogues selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene as well as mixtures thereof. Synthetic vitamin D analogues are more preferred in the compositions according to the invention than naturally occurring vitamin D's or vitamin D derivatives, since the therapeutic effects of the latter may be less selective for the treatment of skin diseases, such as psoriasis.

Further non-limiting examples of vitamin D compounds constituting the first pharmacologically active component A are:

alphacalcidol;

1α-hydroxy-vitamin D2;

1α-hydroxy-vitamin D5;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methyl-1-heptyl)-9,10-secopregna-5(2),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methylhept-1(E)-ene-1-yl-9,10)-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-ethyl-6-hydroxy-1-octyl)-9,10)-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyl-1-octyl)-9,10)-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyloct-1(E)-en-1-yl-9,10)-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-methyl-1'-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'ethyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-hydroxy-1'-hexyloxy-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-ethyl-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10,19-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-(1"-propyl)-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-methyl-1'-pentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3'-hydroxy-3'-methyl-1'-butyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-(5Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-hept-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-hept-1(E)-en-1-yl),9,10-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-ethyl-5'hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z)-7(E),10,19-triene (5'(R) and 5'(S) isomers);

1(S),3(R)-Dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3"(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-(2-hydroxy-2-pentyl)-phenylmethoxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-(3-hydroxy-3-propyl)-phenylmethoxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-trifluoromethyl-5,5,5-trifluoro-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-phenoxymethyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylsulphonylmethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-((1-hydroxy-1-methyl)ethyl)phenylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3,3-difluoro-4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-ethyl-6'-hydroxy-oct-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7'-ethyl-7'-hydroxy-non-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-methoxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20-(4-ethyl-4-hydroxy-1-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20-(5-ethyl-5-hydroxy-1-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19),17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20-(6-ethyl-6-hydroxy-1-octyn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19),17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-4,4-difluoro-5-hydroxy-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4,4-dichloro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4,4-difluoro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-fluoro-4-methyl-pentyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-fluoro-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5-fluoro-5-methyl-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R),20(S)-Trihydroxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-methoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-ethoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-[3-(2-hydroxy-2-methyl-1-propoxy)-prop-1E-en-1-yl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-hydroxy-1-hexylthio)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[5-methyl-5-hydroxy-1-hexylthio] -9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[3-(1-methyl-1-hydroxyethyl)benzylthio]-9,10-seco-pregna-5(Z),7E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-methyl-3-hydroxy-1-butylthio)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-hept-1(E)-en-3-yn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

24-oxo-1(S),3(R),25-Trihydroxy-20(S)-9,10-seco-cholesta-5(Z),7(E),10,19-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-oxo-4-hydroxy-4-ethyl-1-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(5-methyl-5-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hex-2-ynyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpent)-2-yn-1-yloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(3,1-hydroxy-1-methylethyl)phenylmethyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-methyl-1-pentyl) -9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;

1(S),3(R),25-Trihydroxy-(20(S)-9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;

1(S),3(R)-Dihydroxy-(20(S)-(6'-hydroxy-6'-methyl-4'(E)-hepten-1'yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R),22(S),25-Tetrahydroxy-20(R),9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;

22(S)-Ethoxy-1(S)-3(R),25-trihydroxy-10(R)-,9,10-seco-cholesta-5(Z),7(E),10(1,23(E)-tetraene;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenoxymethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenylthiomethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methylpent-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhept-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhepta-1(E),3(E)-dien-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-3-hydroxyprop-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene (24(S) isomer) or the corresponding 24(R) isomer; and

1(S),3(R)-Dihydroxy-20(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers.

As a second pharmacologically active component B it is preferred to use a group I, II or III topical steroid, more preferably a medium to weak acting steroid (groups I and

II). Component B is preferably selected from the group consisting of Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) and esters thereof such as the 21-acetate, 17-adamantoate, 17-benzoate, 17-valerate, and 17,21-dipropionate; Alclomethasone and esters thereof such as the dipropionate; Clobetasole and esters thereof such as the propionate; Clobetasone and esters thereof such as the 17-butyrate; Desoximetasone; Diflucortolon and esters thereof, Diflorasone and esters thereof such as the diacetate; Fluocinonid; Flumetasone and esters thereof such as the pivalate; Fluocinolon and ethers and esters thereof such as the acetonide; Fluticasone and esters thereof such as the propionate; Fluprednidene and esters thereof such as the acetate; Halcinonide; Hydrocortisone and esters thereof such as the -17-butyrate; Mometasone and esters thereof such as the furoate; and Triamcinolon and ethers and esters thereof such as the acetonide; as well as mixtures thereof. More preferred examples of the corticosteroids are Betamethasone or esters thereof such as the 17-valerate or the 17,21-dipropionate, Clobetasole or esters thereof such as the propionate, Triamcinolon or ethers and/or thereof such as the acetonide or the acetonide-21-N-benzoyl-2-methyl-β-alaninate or the acetonide-21-(3,3-dimethylbutyrate), or Hydrocortisone or esters thereof such as the 17-butyrate.

Moreover, the invention relates to a pharmaceutical compositions for dermal use which contain at least one vitamin D or vitamin D analogue and at least one corticosteroid and which exhibits a higher efficacy in the treatment of psoriasis and other inflammatory skin diseases in humans and other mammals than any of the pharmacologically active components used alone. Said efficacy is preferably measured as percentage change in PASI score in psoriasis and related skin diseases, such as sebo-psoriasis and seborrhoic dermatitis.

PASI (Psoriasis Area and Severity Index) score assesses the extent and severity of the patient's psoriasis. The following formulae are used to calculate the PASI score:

Arms 0.2(R+T+S)E=X
Trunk 0.3(R+T+S)E=Y
Legs 0.4(R+T+S)E=Z

Where R=score for redness, T=score for thickness, S=score for scaliness, and E=score for extent where the score is assessed according to a scale from 0 to 4 as follows:

0=no involvement, 1=<10%, 2=10-29&, 3=30-49%, and 4=50-69%. The sum of X+Y+Z gives the total PASI score which can range from 0 to 64.8.

DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graphic illustration of the percentage change in PASI score obtained during 4 weeks of clinical trial where the efficacy of a preparation according to the invention ccontaining calcipotriol hydrate (52.2µg/g) and betamethasone dipropionate (0.643mg/g) is compared to that of a preparation in the same vehicle containing only calcipotriol hydrate (52.2µg/g) and a preparation in the same vehicle of betamethasone dipropionate (0.643mg/g). Fig. 1 shows an efficacy of the preparation of the invention which by far exceeds the efficacy obtainable by the two single component preparations. The change in PASI score reflects in the group of patients treated with the preparation of the invention a success of treatment of psoriasis hitherto unattainable by treatment with commercial preparations containing either calcipotriol or betamethasone, or by alternating treatment with such commercial preparations (cf.) thus proving the advantage of having the two active components present in the same preparation. (EOT=end of treatment).

Fig. 2 is a table showing the figures for percentage change in PASI score at each visit and end of treatment for the same clinical trial as described for Fig. 1.

Fig. 3 is a bar diagram showing percentage of responders as a result of investigators' assessment of overall efficacy at each visit and end of treatment in the same clinical trial as for Fig. 1. Responders are defined as patients with marked improvement or clearance

Fig. 4 is a table showing the figures for percentage of responders as a result of investigators' assessment of overall efficacy at each visit and end of treatment, cf. Fig. 3, in the same clinical trial as for Fig. 1.

TOPICAL FORMULATIONS

In a preferred embodiment the invention provides a topical pharmaceutical composition in the form of an ointment, a cream, a lotion, preferably a scalp lotion, a liniment or other spreadable liquid or semi liquid preparation which is, preferably, non-aqueous or in the form of an oil-in-water or water-in-oil emulsion. In one preferred embodiment, the composition of the invention is a mono-phase composition, i.e. a composition comprising a single solvent system, such as an ointment.

In a further preferred embodiment the invention provides a non-aqueous pharmaceutical composition for dermal use, said composition comprising

a first pharmacologically active component A consisting of at least one vitamin D analogue;

a second pharmacologically active component B consisting of at least one corticosteroid;

the difference between the optimum stability pH of a first pharmacologically active component A and the optimum stability pH of a second pharmacologically active component B being at least 1; and

at least one solvent component C selected from the group consisting of:

(i) compounds of the general formula $R^3(OCH_2C(R^1)H)_xOR^2$ (I) wherein x is in the range of 2-60, R^1 in each of the x units independently is H or CH_3, R^2 is straight chain or branched

C_{1-20}alkyl or benzoyl, and R^3 is H or phenylcarbonyloxy;

(ii) di-(straight or branched)-C_{4-10} alkyl esters of C_4-C_8 dicarboxylic acids;

(iii) straight or branched C_{12-18}-alkyl benzoates;

(iv) straight or branched C_{2-4}-alkyl esters of straight or branched C_{10-18}-alkanoic or -alkenoic acids;

(v) propylenglycol diesters with C_{8-14}-alkanoic acids; and

(vi) branched primary C_{18-24} alkanols, and

wherein components A and B are as defined above.

It has been found that in such combination compositions containing a solvent component C, the active components can co-exist without degradation, despite their different pH/stability profiles. The tendencies of the active compounds to affect one another with regard to pH is minimised or eliminated.

It is preferred that the maximum difference in optimum stability pH between the pharmacologically active compounds is at least 1.5, more preferred at least 2, in particular at least 2.5, more particularly at least 3, especially at least 4, such as at least 5.

In the general formula (I) defined above, it is preferred that the factor x (which designates the number of the units within the parentheses) is in the range 4-50, more preferably 4-40, in particular 4-30, especially 5-25, more especially 10-20, such as about 15. It is further preferred that R^1 is CH_3.

It is preferred that said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) where R^1, x, and R^2 are as defined above, and mixtures thereof.

As non-limiting specific examples of the types (i)-(vi) of the solvent component C defined above may be mentioned the following, including trade names:
Arlamol E (polyoxyethylene(15) stearyl ether);
Arlamol DoA (diisooctyl ester of adipic acid);
Arlasolve 200 (Polyoxyethylene-20-isohexadecyl ether);
Eutanol G (2-octyldodecanol);
Finsolv (Isostearyl benzoate);
Finsolv P (polyoxypropylene-15-stearyl ether benzoate);
Isopropylesters of straight or branched C_{10} - C_{18} alkanoic or alkenoic acids such as isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate and isopropyl monooleate;
Miglyol 840 (Propylene glycol diester of caprylic and caprinic acid);
DPPG (propylene glycol dipelagonate);
Procetyl AWS ($CH_3(CH_2)_{14}CH_2(OCH(CH_3)CH_2)_5$-$(OCH_2)_{20}OH$).

The compositions of the present invention may be prepared in accordance with methods well known to the person skilled in the field of pharmacy. Thus, the non-aqueous compositions may be prepared by incorporating the components into a well known ointment or lotion base excipient such as white soft paraffin (also known as vaseline) or Plastibase™ (a base prepared from polyethylene (average MW about 21,000) and paraffin liquid) or ESMA-P™ (a microcrystalline wax). As an example, preparation of a composition according to the invention is typically performed by melting white soft paraffin, adding a solution (typically at a concentration in the range of 0.0005-2.5% w/w) of the vitamin D analog in the required amount of solvent component C, e.g. Arlamol E, followed by addition of a dispersion of the corticosteroid component B in paraffin oil, typically with a particle size of from 0.1 to 20 μm, and then cooling the mixture. Typical content ranges of the various components in the finished composition according to the invention are 0.005 to 0.1 %w/w of the corticosteroid component B, from 0.0001 to 0.025 %w/w of the vitamin D analog component A, and from 1 to 20% w/w of the solvent component C, the remainder typically being primarily base excipient such as the above-mentioned white soft paraffin and/or paraffin oil. The composition may also contain other commonly used additives such as antioxidants (e.g. α-tocopherol).

The composition according to the invention provides the following therapeutic advantages in the treatment of skin diseases, such as psoriasis, sebo-psoriasis and related disorders, compared to the single compound therapy or combination therapy of the prior art:

- A clinical investigation has showed that treatment of psoriasis patients with a composition according to the invention comprising calcipotriol and betamethasone resulted in a faster onset of healing and a more effective healing of plaques than patients treated with only one of the active compounds.
- A composition combining a vitamin D analogue and a topical steroid provides synergy in the form of additional benefit to the patient apart from the direct therapeutic value of the active substances. It has been shown that the skin irritative side effects of a vitamin D analogue, such as calcipotriol, is alleviated by

the simultaneous application of a steroid, such as betamethasone, onto psoriatic skin, an effect that is only attainable using a two-component or multi-component treatment regimen where a vitamin D analogue and a steroid cannot be applied simultaneously to affected skin due to incompatibility of the praparations. When both a vitamin D analogue and a topical steroid are used in a combination treatment of psoriasis it has hitherto been necessary to use separate applications, typically one in the morning and the other in the evening, making it impossible to obtain any synergistic effect of the two types of active compounds (cf. Ortonne, J.P., Nouv. Dermatol., 1994, 13(10), p. 746-751), or where a certain degree of synergistic effect, such as less skin irritation, has been reported for a two-component regiment (cf. Kragballe, K. et al. *Br J Dermatol* 1998 Oct;139(4):649-54, and Ruzicka, T. et Lorenz, B. *Br J Dermatol* 1998, 138(2), 254-58) a substantial proportion of psoriasis patients will not benefit due to non-compliance with the treatment regimen.

- Satisfactory medical treatment of skin disorders, such as psoriasis, can be attained in a shorter period of time using the composition according to the invention resulting in a reduction of steroid side effects, such as skin atrophy and rebound. Besides, it can be anticipated that even a milder acting steroid of group I, such as hydrocortisone which is presently not administered for psoriasis treatment, will be efficient in reducing or even eliminating the skin irritation which often follows calcipotriol treatment.
- Thus, the tolerance of the treatment will be considerably improved due to reduction of side effects of the active compounds.
- Instructions for treatment will be simpler when a single preparation is needed resulting in improved compliance for the patient and the possibility of efficient tretment of a much larger population of psoriasis patients.
- Instructions for treatment will be simpler when a single preparation is needed resulting in improved safety for the patient.

The invention also relates to a preferred pharmaceutical preparation according to the invention which is especially useful for the treatment of psoriatic skin diseases which are complicated by additional fungal infections, and which further contains an anti-

fungal agent selected, e.g., from the group consisting of miconazol, clotrimazol, terbinafin, ciclopirox, bifonazol, nystatin, ketoconazol, econazol, and amorolfine.

Preferably, the compositions according to the invention do not contain other therapeutically effective compounds selected from the group consisting of the xanthine derivatives pentoxifylline, propentofyllin, and torbafylline, or any other xanthine or xanthine derivative.

The invention also relates to a method of treatment of psoriasis and related skin diseases comprising topically administering an effective amount of a composition according to the invention to a patient in need of such treatment. Said method preferably comprises topical administration once or twice daily of a medically sufficient dosage of said composition.

The composition according to the invention preferably contains 0.001-0.5mg/ g or ml or more preferably 0.001-0.25mg/g or ml of said component A and 0.05-0.1mg/g or ml of said component B.

The invention is further illustrated by the following, non-limiting examples.

EXAMPLE 1

Ointment containing Calcipotriol and Betamethasone dipropionate

919,3 g of White Soft Paraffin is melted at 80°C followed by cooling to 70°C and maintaining that temperature. Thereafter, 52.2 mg Calcipotriol hydrate (50 mg Calcipotriol) is dissolved in 50 g Arlamol E (polyoxypropylene-15-stearyl ether) to form a solution (Solution 1). Solution 1 is then added slowly into the molten paraffin while stirring.

Betamethasone (0,5 g, in the form of 0.643g of its dipropionate) in particulate form (99% <15μm) is dispersed in 30 g Paraffin Liquid to form Dispersion 1. Dispersion 1 as well as 20 mg α-tocopherol are added to the Calcipotriol-containing paraffin

mixture of while stirring, after which the mixture is cooled to below 30°C to give a composition according to the invention with the following composition:

1g of ointment contains:	Betamethasone (as dipropionate 0.643 mg)	0.5mg
	Calcipotriol (as hydrate 52.2 µg)	50 µg
	Paraffin, Liquid	30 mg
	Polyoxypropylene-15-Stearyl Ether	50 mg
	α-Tocopherol	20 µg
	White Soft Paraffin....to make	1 g

EXAMPLE 2

Stability test

The chemical stability of the two active components was tested after storage for 1 month at 40°C and 3 months at 25°C and 40°C, respectively.The quantitative content of Calcipotriol was determined by HPLC.

The Calcipotriol was extracted from the preparation into a mixture of methanol and 0.01M diammonium hydrogenphosphate (70:30) and quantified under the following HPLC conditions: Column: about 125 mm ∅ 4 mm (i.d.) stainless steel column with LiChrospher RP-18, 5 µm; mobile phase: acetonitrile-methanol-0.01 M aqueous ammonium phosphate pH 6 (20:50:30); flow: about 2 ml/min; detection: variable wavelength UV-detector set at 265 nm. Calcipotriol and the related substances were separated by the reverse phase HLPC-method described above; Column: Superspher RP-18, 4 µm; Flow: 1.2 ml/min. The quantitative content of Betamethasone Dipropionate was determined by HLPC.

The Betamethasone Dipropionate was extracted from the preparation into a mixture of acetonitrile:water (50 : 55) and quantified under the following HPLC conditions: Column: About 125 mm ∅ 4 mm (i.d.) stainless steel column packed with LiChrospher RP-18, 5µm. Mobile phase: Acetonitrile: water (50 : 55). Flow: 2 ml/min. Detection: Variable wavelength UV-detector set at 240 nm. The related substances besides betamethasone were determined by a reverse phase HLPC-method analogous to the

above. Betamethasone: Determined as above with the exception of the mobile phase: Acetonitrile/methanol/0.05M buffer pH7 (25:5:70).

The results are shown in the following Table 1.

Table 1

	Calcipotriol µg/g	Calcipotriol-related substances %	Betamethasone dipropionate mg/g	Betamethasone-related substances %
Start	50.0	1.6	0.63	1.2
25°C				
3 months	50.5	1.4	0.64	0.2
40°C				
1 month	48.0	2.1	0.64	0.6
3 months	49.7	1.8	0.64	0.2

It will be seen from Table 1 that both Calcipotriol and Betamethasone ester are very stable under the test conditions.

The stability of Calcipotriol was compared to an similar ointment where propylene glycol was used as the solvent and lanolin used as an emulsifier. The composition of the comparison ointment was the same as the above with respect to Calcipotriol and Betamethasone dipropionate, as well as 10% w/w propylene glycol, 10% w/w anhydrous lanolin and 80% w/w White Soft Paraffin. The comparison ointment was stored for 2.5 months at 5°C and 40°C, respectively. Only the content of Calcipotriol-related substances was determined in the manner described above. The results are shown in Table 2.

Table 2

	Calcipotriol related substances %
5°C	20
40°C	96

As it will be seen from the results, Calcipotriol is degraded almost completely in the comparison composition under the test conditions as opposed to a composition of the invention, where the Calcipotriol is retained with essentially no degradation.

EXAMPLE 3

Medical skin lotion comprising a two phase solvent system

1 g contains:

Betamethasone (As Dipropionate 0,643 mg)	0.5 mg
Calcipotriol (as Hydrate 52.2 µg)	50 µg
Disodium Phosphate Dihydrate	2.5 mg
Diazolidinyl Urea	3 mg
Polyoxypropylene-15-Stearyl Ether (Arlamol® E)	50mg
Isohexadecan (Arlamol® HD)	200 mg
Polyoxyethylene-2-Stearyl Ether (Brij® 72)	30 mg
Water, purified ....to make	1 g

Procedure for the preparation of 1 kg of lotion:

2.5 g Disodium Phosphate and 3 g Diazolidinyl Urea are dissolved in about 714 g water. The solution is heated to 60 - 70°C to obtain the water phase. 30 g Polyoxyethylene-2-Stearyl Ether is melted together with 200 g Isohexadecan at 60 - 70°C and a solution of 52.2 mg Calcipotriol Hydrate in 50 g Polyoxypropylene-15-Stearyl Ether is added to obtain the oil phase. The two phases are mixed during homogenisation, 643 mg Betamethasone Dipropionate is dispersed into the mixture, and the lotion is cooled during mixing to room temperature. The preparation is stable at 25°C for > 14 days.

Claims

1. A pharmaceutical composition for dermal use, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid.
2. A composition according to the preceding claim which further comprises at least one pharmaceutically acceptable carrier, solvent, or diluent.
3. A composition according to claim 1 or 2 wherein said vitamin D analogue is selected from the group consisting of seocalcitol; calcipotriol; calcitriol; tacalcitol, maxacalcitol; paricalcitol; falecalcitriol; 1α,24S-dihydroxy-vitamin D2; and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.
4. A composition according to the preceding claims wherein said vitamin D analogue is selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.
5. A composition according to any one of the preceding claims wherein the vitamin D analogue is effective against psoriasis and related disorders of the skin in humans and other mammals.
6. A composition according to the preceding claim wherein said vitamin D analogue is calcipotriol or its hydrate.
7. A composition according to any one of the preceding claims wherein said corticosteroid is selected from the group consisting of Betamethasone, Clobetasol, Clobetasone, Desoximethasone, Diflucortolon, Diflorasone, Fluocinonid, Flumethasone, Fluocinolon, Fluticasone, Fluprednidene, Halcinonide, Hydrocortisone, Momethasone, Triamcinolon, and pharmaceutically acceptable esters and acetonides as well as mixtures thereof.
8. A composition according to the preceding claim wherein said esters or acetonides are selected from the group consisting of 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl-β-alaninate, acetonide-21-(3,3-dimethylbutyrate), and 17-butyrate.

9. A composition according to claim 1-6 wherein said corticosteroid is selected from the group consisting of medium to weak acting corticosteroids.

10. A composition according to the preceding claim wherein said corticosteroid is Hydrocortisone or its 17-butyrate ester.

11. A composition according to any one of the preceding claims in the form of a mono-phase composition.

12. A composition according to the preceding claim which is an ointment.

13. A composition according to the preceding claim essentially as described in Example 1 herein.

14. A composition according to any one of claims 1 to 10 which is a lotion.

15. A composition according to the preceding claim essentially as described in Example 3 herein.

16. A composition according to any one of the preceding claims exhibiting a higher efficacy in the treatment of psoriasis and related skin disorders in humans and other mammals than the efficacy attainable when using any composition comprising said components A or B alone.

17. A composition according to the preceding claim where said efficacy is measured as percentage change in PASI score.

18. A composition according to claim 1or 2, characterised in that the difference between the optimum stability pH of said first component A and the optimum pH of said second component B is at least 1; and at least one solvent component C selected from the group consisting of:

(i) compounds of the general formula $R^3(OCH_2C(R^1)H)_xOR^2$ (I) wherein x is in the range of 2-60, R^1 in each of the x units independently is H or CH_3, R^2 is straight chain or branched

C_{1-20}alkyl or benzoyl, and R^3 is H or phenylcarbonyloxy;

(ii) di-(straight or branched)-C_{4-10} alkyl esters of C_4-C_8 dicarboxylic acids;

(iii) straight or branched C_{12-18}-alkyl benzoates;

(iv) straight or branched C_{2-4}-alkyl esters of straight or branched C_{10-18}-alkanoic or -alkenoic acids;

(v) propylenglycol diesters with C_{8-14}-alkanoic acids; and

(vi) branched primary C_{18-24} alkanols; and

wherein compounds A and B are as defined above.

19. A composition according to the preceding claim wherein said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) where R^1, x, and R^2 are as defined in claim 18, and mixtures thereof.

20. A composition according to the preceding claim where R^1 is CH_3.

21. A composition according to claim 19 wherein said component C is polyoxypropylene-15-stearyl ether.

22. A pharmaceutical composition according to any one of claims 18-21 wherein said second component B is selected from the group consisting of Betamethasone, Clobetasol, Clobetasone, Desoximethasone, Diflucortolon, Diflorasone, Fluocinonid, Flumethasone, Fluocinolon, Fluticasone, Fluprednidene, Halcinonide, Hydrocortisone, Momethasone, Triamcinolon, and pharmaceutically acceptable esters and acetonides as well as mixtures thereof.

23. A pharmaceutical composition according to any one of claims 18-22 wherein said esters are selected from the group consisting of 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl-β-alaninate, acetonide-21-(3,3-dimethylbutyrate), and 17-butyrate.

24. A composition according to any one of claims 18-23 wherein said first component A is selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.

25. A composition according to any one of the preceding claims containing 0.001-0.25mg/g or ml of said component A and 0.05-0.1mg/g or ml of said component B.

26. A pharmaceutical preparation according to any one of the preceding claims which further contains an anti-fungal agent preferably selected from the group consisting of miconazol, clotrimazol, terbinafin, ciclopirox, bifonazol, nystatin, ketoconazol, econazol, and amorolfine.

27. A pharmaceutical preparation according to any one of the preceding claims which does not contain a xanthine derivative selected from the group consisting of pentoxifylline, propentofyllin, and torbafylline, or any other xanthine or xanthine derivative.

28. Use of a composition according to any one of the preceding claims for the topical treatment of psoriasis and related skin disorders in humans and other mammals.

29. Method of treatment of psoriasis and related skin diseases comprising topically administering an effective amount of a composition according to any one of claims 1-27 to a patient in need of such treatment.

30. Method according to the preceding claim comprising topical administration once or twice daily of a medically sufficient dosage of said composition.

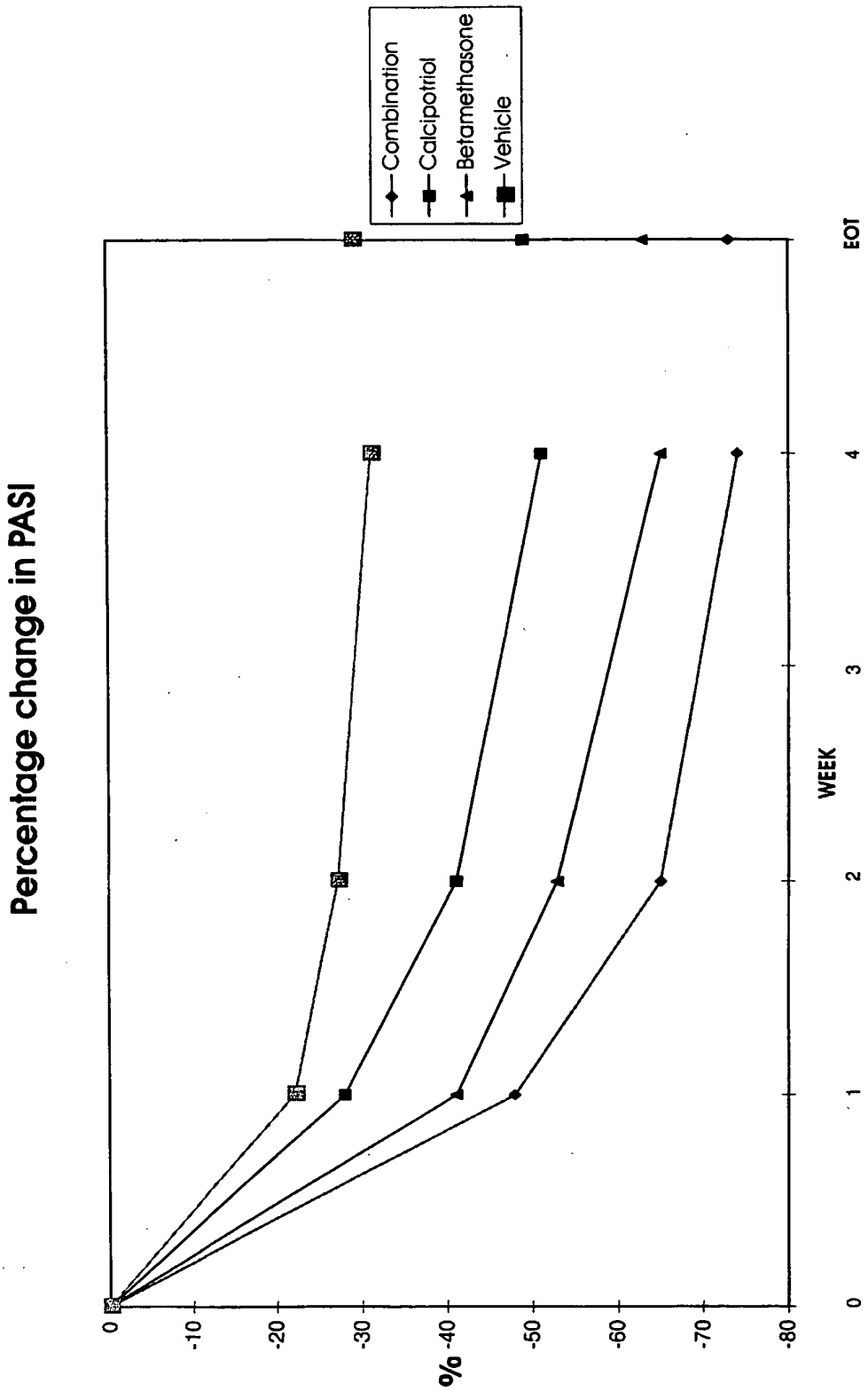
Combination
Calcipotriol
Betamethasone
Vehicle
Percentage change in PASI
0
-10
-20
-30
-40
-50
-60
-70
-80
%
0
1
2
3
4
EOT
WEEK

FIGURE 1

Percentage change in PASI score at each visit and end of treatment

Percentage change in PASI score	COMB (n=301)	CALC (n=308)	BETA (n=312)	VEHICLE (n=107)
Visit 1				
Mean	10.9	10.9	10.7	10.6
Percentage change				
To visit 2				
Mean	-48.1	-28.4	-41.4	-21.5
To visit 3				
Mean	-64.9	-40.8	-53.2	-27.4
To visit 4				
Mean	-73.9	-51.3	-64.5	-31.3
To end of treatment				
Mean	-73.2	-48.8	-63.1	-28.8

FIGURE 2

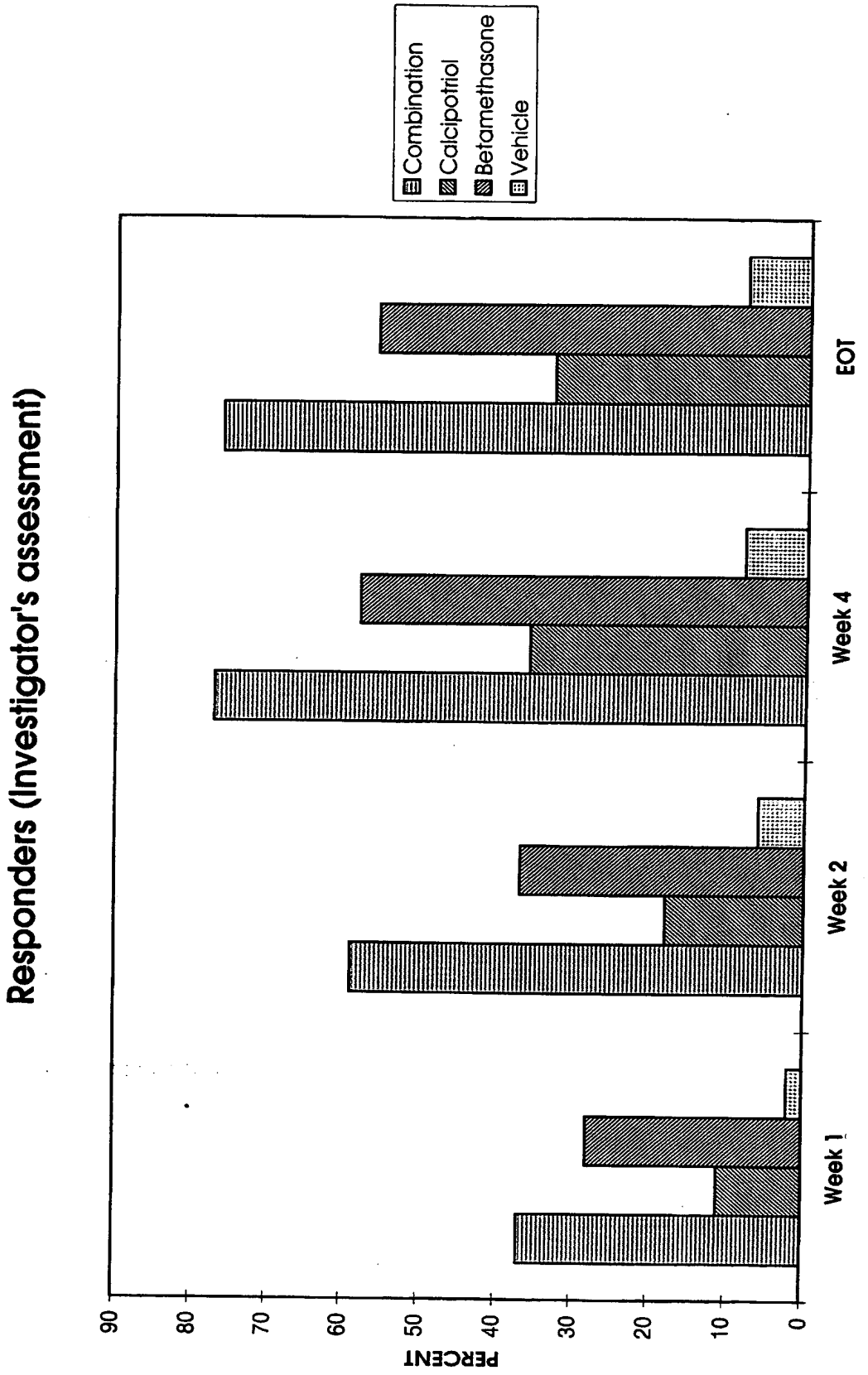
Responders (Investigator's assessment)
Combination
Calcipotriol
Betamethasone
Vehicle
PERCENT
0
10
20
30
40
50
60
70
80
90
Week 1
Week 2
Week 4
EOT

FIGURE 3

Investigator's assessment of overall Efficacy at each visit and end of treatment

Investigator's overall efficacy assessment	COMB (n=301) %	CALC (n=308) %	BETA (n=312) %	VEHICLE (n=107) %
Visit 2				
Non responder	63.5	89.5	72.5	98.1
Responder	36.5	10.5	27.5	1.9
Total	100.0	100.0	100.0	100.0
Visit 3				
Non responder	41.5	82.2	62.7	94.2
Responder	58.5	17.8	37.3	5.8
Total	100.0	100.0	100.0	100.0
Visit 4				
Non responder	23.1	64.4	42.4	91.9
Responder	76.9	35.6	57.6	8.1
Total	100.0	100.0	100.0	100.0
End of treatment				
Non responder	23.9	66.6	44.2	92.5
Responder	76.1	33.4	55.8	7.5
Total	100.0	100.0	100.0	100.0

FIGURE 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 00/00033

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/59 A61K31/56 A61K31/593 A61K31/573 A61P17/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERN. FILE CAPLUS [Online] ; GLADE C P ET AL: "Epidermal cell DNA content and intermediate filaments keratin 10 and vimentin after treatment of " retrieved from CAPLUS , accession no. 1996:599855 Database accession no. 125:266250 XP002900974 abstract & BR. J. DERMATOL., vol. 135, no. 3, 1996, pages 379-384, ---	1-30
X	WO 94 14453 A (LEO PHARM PROD LTD ;SERUP JORGEN VEDELSKOV (DK)) 7 July 1994 (1994-07-07) page 22, line 15 -page 24, line 17; claims; figures 1-3 --- -/--	1-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

°A° document defining the general state of the art which is not considered to be of particular relevance

°E° earlier document but published on or after the international filing date

°L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

°O° document referring to an oral disclosure, use, exhibition or other means

°P° document published prior to the international filing date but later than the priority date claimed

°T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

°X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

°Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

°&° document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2000	15. 06. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell/eö

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 00/00033

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 129 003 A (YISSUM RES DEV CO) 27 December 1984 (1984-12-27) page 6, line 3 - line 9 page 11, line 13 - line 22 page 13; claims	1-30
X	RUZICKA T ET AL: "Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicentre, doucle-blind, randomized study" BRITISH JOURNAL OF DERMATOLOGY, vol. 138, 1998, pages 254-258, XP002900975 page 257	1-30
A	WO 94 15912 A (LEO PHARM PROD LTD ;HANSEN ERIK TORNGAARD (DK); RASTRUP ANDERSEN N) 21 July 1994 (1994-07-21) the whole document	1-30
A	WO 91 12807 A (LEO PHARM PROD LTD) 5 September 1991 (1991-09-05) the whole document	1-30
A	US 5 087 620 A (PARAB PRAKASH) 11 February 1992 (1992-02-11) the whole document	1-30
A	US 5 886 038 A (ROSENBERG E WILLIAM ET AL) 23 March 1999 (1999-03-23) the whole document	1-30
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A	EP 0 544 391 A (TEVA PHARMA ;UNIV RAMOT (IL)) 2 June 1993 (1993-06-02) page 8, line 29 -page 9, line 37; claims	1-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00033

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28-30
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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Claims 28-30 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 00/00033

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INTERNATIONAL SEARCH REPORT

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